IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Hiroharu MATSUOKA et al
Application No.: 09/890,219
Filed: December 12, 2001
For: SUBSTITUTED PHENETHYLAMINE DERIVATIVES

Confirmation No. 7465
Art Unit: 1625
Examiner: B. M. Robinson

DECLARATION

Honorable Commissioner of Patent and Trademarks
P.O.Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Tsutomu SATO, a Japanese citizen, residing at 236-51, Kawashimata, Gotemba-city, Shizuoka-prefecture, Japan, hereby solemnly and sincerely declare and state that:

I am one of the applicants of the above-identified patent application;

I was awarded a master degree in Pharmaceutical Science in 1991 from the Faculty of Pharmaceutical Science, Tohoku University, Miyagi-prefecture, Japan;

I have been employed by Chugai Pharmaceutical Co. Ltd., the assignee of the present application, since 1991, and have worked at Fuji Gotemba Research Laboratories in Gotemba, as a researcher of medicinal chemistry field during the entire period.

I declare further that I engaged as a researcher in research into motilin receptor antagonists.

I declare further that I have read all of the Official Actions in the above-identified application, and have read, and am familiar with each of the references cited in the Official Action by the Examiner.

Purpose of this declaration

The assignee limited the definitions of R_7, $R_{7'}$, $R_{7''}$, R_{11}, $R_{11'}$, $R_{11''}$, $R_{11'''}$, R_{14}, and R_{15}

of the compounds of the present invention, by the amendment filed in response to the Official Action dated June 20, 2007. Further, the assignee deleted a hydrate of the compounds of present invention from all of the claims. The purpose of this declaration is to show that, although the present specification does not provide experimental results of motilin receptor binding assay for all of the compounds of the present invention after the amendments, some of the compounds whose experimental binding assay results are not provided in the present specification actually have an activity of binding to a motilin receptor, and that this fact supports that the present invention meets the enablement requirement, based on the following experimental data.

I declare that the following tests were conducted at my direction or under my supervision, and that the test results are true and correct to the best of my knowledge.

Method of experiments

A motilin receptor binding assay was conducted for the compounds of examples 5-7, 10, 11, 13, 18, 20, 45, 46, 48, 65, 68, 69, 74, 116, 138, 146, 150A, 153, 159, 161, 174-176, 177B, 178B and 179A, using the following method [please refer to Vantrappen et al, Regul. Peptides, 15, 143 (1986)].

A duodenum was taken from a killed rabbit, mucosa was stripped from it, and homogenized in a 50mM Tris solution to afford a protein solution. A portion of the protein solution was incubated with a 25pM ^{125}I labeled motilin solution (blank), then a radio activity of the radio active compound bound to the protein was determined. Differences between a radio activity obtained from the blank solution and that obtained by adding a large excess amount of motilin (10^{-7}M) to the blank solution, was regarded as a specific binding. Next, a portion of the protein solution was supplemented with any one of the example compounds at predetermined concentrations, and incubated with a 25pM ^{125}I labeled motilin solution, then a radio activity of the radio active compound bound to the protein was determined. A motilin antagonistic activity of the example compounds was expressed as a concentration at which the specific binding was reduced to 50% (IC_{50}, nM). Results are shown below.

Results

Table 1

Example No.	Motilin receptor binding

	assay
	IC_{50}(nM)
5	12
6	43
7	2.3
10	15
11	0.41
13	0.56
18	0.41
20	2.1
45	44
46	8.3
48	51
65	81
68	69
69	13
74	10
116	90
138	4.9
146	4.4
150A	22
153	1.4
159	11
161	15
174	0.51
175	60
176	1.8
177B	22
178B	5.3
179A	0.52

Conclusion

As shown in Table 1, for the example compounds of the present invention, for which the present specification does not provide motilin receptor binding assay results, a motilin receptor binding activity was confirmed. Thus, it is reasonable to conclude that those skilled in the art would consider that other compounds of the present invention similar to these examples also have a motilin receptor binding activity. Additionally, by the amendment filed in response to the Official Action dated June 20, 2007, the assignee deleted a hydrate of the compounds of the present invention from all of the claims, and limited the definitions of R_7, $R_{7'}$, $R_{7''}$, R_{11}, $R_{11'}$, $R_{11''}$, $R_{11'''}$ and R_{14}. Thus, the present specification is considered to more sufficiently support the present invention than before amendment.

Therefore, by the response, I believe that the enablement rejection has been resolved.

Dated this 15th day of October, 2007

Tsutomu Sato

Tsutomu Sato